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Market Measures, Inc

OCHRONOSIS STUDY

Final Report

Prepared For:

NDMA

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OCHRONOSIS RECALL SURVEY

PURPOSE

This Ochronosis Recall Survey was suggested by the Food and Drug Administration in order to compile non-documented reports of cases of ochronosis and antecedent exposure to skin-lightening agents over the life-time medical practices of members of the American Association of Dermatology (AAD). Ochronosis is a rare bluish gray discoloration of the skin, usually on the face of darker pigmented individuals. Over the last 20 years, skin lighteners have been marketed in the U.S. in a variety of formulations, including various strengths of hydroquinone, various forms of hydroquinone, non-hydroquinone ingredients (e.g., mercury) etc. from both domestic and foreign sources.

This study is unique and distinctly different from other market surveys conducted by Market Measures Inc. in that each physician was asked to report recall and frequency of a rare condition over the entire lifetime of his/her practice. In all other surveys based on recall conducted by Market Measures Inc. over the 25 years that Market Measures Inc. has been active in survey research, the longest previous recall period has been one year.

Additionally, hydroquinone manufacturers and distributors that are members of NDMA and represent about 70% of the hydroquinone marketplace initiated significant labeling changes on May, 1992. This consumer labeling emphasizes discrete usage of OTC hydroquinone products (see Appendix A). No attempt was made to distinguish consumer vs. patient usage of OTC and Rx product or usage prior to and after the initiation of the labeling changes, since (a.) no attempt was made to obtain the available medical records (i.e., to confirm exposure); and (b.) the OTC label has not been on OTC hydroquinone products for a sufficiently long period to affect the survey results.

No attempt was made to create an "incidence figure" for ochronosis by this survey. This is because of the nature of the recall (i.e., over full length of medical practice spanning many years), lack of confirmation of diagnosis, lack of confirmation of reported drug exposure either by medical records or patient interview, no determination of coincident cases among reporting physicians, etc.

METHODS

A questionnaire (Appendix B) was developed by NDMA's Hydroquinone Task Group in association with the AAD Committee on Therapeutics. The questionnaire was one page in length and provided the responding physician with a description of endogenous and exogenous ochronosis and asked their recall of the number of cases of ochronosis they have treated in the history of their medical practice. Those physicians who had treated exogenous ochronosis were asked additional questions including dates of diagnosis, methods of diagnosis and agents reportedly associated with the condition. No independent confirmation of diagnosis or of reported drug exposure was undertaken as part of this survey.

The survey was mailed to the entire universe of AAD members in cooperation with the AAD. No incentive was included for participation, at the request of AAD. It was, however, made clear to the respondent that the project was endorsed by the AAD.

The questionnaire was mailed on February 26, 1993 to the universe of AAD members, which number 6,500. A second mailing of 5,027 questionnaires was completed on March 24, 1993 and went to all physicians who had not yet responded. The field closed on April 23, 1993.

The following report consists of responses from 2,108 dermatologists, representing a response rate of 32%. Market Measures Inc. conducted the survey and compiled the responses.

SIGNIFICANT FINDINGS

1. This survey covers responses from 2,108 physicians representing 32% of all AAD members, who report a collective current practice of over 44 million patients. The median length of practice was 12 years (range: 1 to >46 years). (Table 1)

2. 1,886 of responding dermatologists (89%) reported no diagnosis of exogenous ochronosis in their patients seen over a median practice length of 12 years. (Table 1)

3. 222 dermatologists reported diagnosing $\geq$ 1 cases of exogenous ochronosis during their life-time practices (median 12 years; total of 512 reported cases). From the survey, it is unknown how many of these reported cases were seen by more than one physician. (Table 1)

4. Among the reported cases (i.e., n = 512), 46 cases were reportedly associated with 2% hydroquinone and "OTC bleaching creams," and 250 cases with Rx or unspecified types of hydroquinone products. The remaining 216 cases were reportedly due to sources other than hydroquinone (i.e., other drugs, metals, disease, etc.). (Table 2)

   Market research information from hydroquinone manufacturers indicated that hydroquinone (HQ) products have, over the years, been distributed/prepared from a number of sources, including: physician dispensed prescription HQ; prescription HQ; pharmacist compounded HQ products of unknown composition; OTC 2% HQ products; OTC greater than 2% HQ products; cosmetics; imported products of unknown composition (e.g., mercury plus HQ in combination); etc. Misclassification of drug exposures due to errors in recall/reporting are therefore of concern.

5. Virtually no physicians reviewed their records for the purpose of this survey. Physicians report the availability of records in about 40% of the exogenous ochronosis cases. (Table 3)

6. 130 of physicians diagnosing cases of exogenous ochronosis stated they obtained biopsies for definitive diagnosis in some or all of their cases. There is no independent review or confirmation of these reports by the survey. (Table 4)

7. Responding physicians who report that they have diagnosed exogenous ochronosis have a higher proportion of black patients in their practice. Physicians who report diagnoses of ochronosis report 15% of their patient population to be black versus 10% for the total responding physician population. (Table 5)

Tabular compilations of these summary findings appear on the following pages. Appendix C contains tabular summaries of certain additional secondary data (see List of Tables, next page).

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Text Tables:

Appendix C Tables:

TABULAR COMPILATIONS

1. This survey covers responses from 2,108 physicians representing 32% of all practicing dermatologists, who report a collective current practice of over 44 million patients. The median length of practice was 12 years (range: 1 to >46 years). (Table 1)

2. 1,886 of responding dermatologists (89%) reported no diagnosis of exogenous ochronosis in their patients seen over an median practice length of 12 years. (Table 1)

3. 222 dermatologists (11%) reported diagnosing one or more cases of exogenous ochronosis during their median practice length of 12 years for a total of 512 reported cases. There are no data from the survey to determine how many of these reported cases were seen by more than one physician. (Table 1)

Table 1: Number of Patients in Practice: Percentage of Physicians Who Have and Have Not Treated Cases of Exogenous Ochronosis.

No. Patients In Practice	Total Physicians %	MDs Who Have Dx/Tx One/More Cases of Exog. Och. %	MDs Who Have Not Dx/Tx Exog. Och. %
< 1,000	2	2	2
1,000-4,999	10	12	10
5,000-9,999	10	8	11
10,000-14,999	9	7	9
15,000-19,999	6	4	6
20,000-29,999	9	12	9
30,000-49,999	8	8	7
≥ 50,000	6	7	6
No Answer	40	40	40
	100	100	100
Median Number Patients	13,000	15,000	13,000
Base: Total MDs	(2,108)	(222) (11%)	(1,886) (89%)
Median Yrs in Practice *	12	11	12

* See also Appendix C Tables C-1 and C-2

4. Among the reported cases (i.e., n = 512), 46 cases were reportedly associated with 2% hydroquinone and "OTC bleaching creams," and 250 cases with Rx or unspecified types of hydroquinone products. The remaining 216 cases were reportedly due to sources other than hydroquinone (i.e., other drugs, metals, disease, etc.). (Table 2)

Table 2: Agents Reportedly Associated with Exogenous Ochronosis: Percentage of Physicians Who Have Reportedly Diagnosed/Treated One or More, Two or More, Five or More Cases of Exogenous Ochronosis.

Reported Exposure	MDs Who Reportedly Diagnosed/ Treated:		
"HYDROQUINONE"	≥1 Cases %	≥2 Cases %	≥5 Cases %
No Brandname 2% HQ	2	3	3
Brandname OTC 2% HQ	3	1	-
Brandname Rx HQ	3	3	-
"HQ 4%"	<0.5	-	-
* Unspecified HQ	41	41	39
"BLEACHING CREAMS": No Ingredient Reported			
OTC Bleaching Creams	4	3	2
Unspecified Bl. Creams	5	5	3
OTHER UNSPECIFIED SOURCES:			
Drugs	14	15	20
Cosmetics	5	7	13
Elements/chemicals	4	5	2
Disease/conditions	3	4	3
Others (net)	4	4	6
Unknown	2	1	-
Did Not Remember	1	<0.5	-
No Answer	8	8	9
	100	100	100
Base (Exogenous Cases)	(512)	(394)	(216)

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* Sources of unspecified hydroquinone include: physician dispensed prescription HQ; prescription HQ; pharmacist compounded HQ products of unknown composition; OTC 2% HQ products; OTC greater than 2% HQ products; cosmetics; misclassified exposures due to errors in recall/reporting; imported products of unknown composition (e.g., mercury plus HQ in combination); etc.

5. Virtually no physicians reviewed their records for the purpose of this survey. Physicians report that medical records are available in approximately 40% of the exogenous ochronosis cases. (Table 3)

Table 3: Physician Involvement in Exogenous Cases (Attending Physician, Medical Records, Review of Medical Records for Survey): Percentage of Physicians Who Have Reportedly Diagnosed/Treated One or More, Two or More, Five or More Cases of Exogenous Ochronosis.

Parameter	MDs Who Reportedly Diagnosed/Treated:		
Respondent as the Only Attending Physician:	≥1 Cases %	≥2 Cases %	≥5 Cases %
Yes	52	52	57
No	44	44	32
No Answer	4	4	11
	100	100	100
Medical Records Available:	%	%	%
Yes	40	40	53
No	52	52	43
No Answer	8	8	4
	100	100	100
Records Reviewed for Survey:	%	%	%
Yes	2	-	-
No	95	97	96
No Answer	3	3	4
	100	100	100
Base (Total MDs):	(222)	(104)	(28)

6. 130 of physicians diagnosing cases of exogenous ochronosis stated they obtained biopsies for definitive diagnosis in some or all of their cases. There is no independent review or confirmation of these reports by the survey. (Table 4)

Table 4: Number of Exogenous Cases Reportedly Confirmed by Biopsy: Percentage of Physicians Who Have Reportedly Diagnosed/Treated One or More, Two or More, Five or More Cases of Exogenous Ochronosis.

	MDs Who Reportedly Diagnosed/Treated:		
Number of Biopsies:	≥1 Cases %	≥2 Cases %	≥5 Cases %
0	36	36	28
1	40	18	11
2	14	31	25
3	2	5	4
≥5	2	3	14
No Answer	6	7	18
	100	100	100
Median Number	1	1	2
Base (Total MDs)	(222)	(104)	(28)

7. Responding physicians who report that they have diagnoses exogenous ochronosis have a higher proportion of black patients in their practice. Physicians who report diagnoses of ochronosis report 15% of their patient population to be black versus 10% for the total responding physician population. (Table 5)

Table 5: Patient Demographics: Patient Racial/Ethnic Group by Percentage of Physicians Who Have or Have Not Diagnosed Cases of Exogenous Ochronosis.

Patient Racial Ethnic Group	Total Physicians %	MDs Who Have Dx/Tx Exog. Cases %	MDs Who Have Not Dx/Tx Endog. Cases %
White	79	73	80
Black	10	15	10
Hispanic	6	8	6
Asian	4	4	4
	100	100	100
Base (Total MDs)	(2,106)	(222)	(1,884)

APPENDIX A

NDMA Hydroquinone Task Group
Voluntary Labeling Guidelines

Nonprescription Drug Manufacturers Association

Hydroquinone Task Group

Voluntary Labeling Guidelines
May 1992

The manufacturers and distributors of 2% hydroquinone-containing OTC skin discoloration fade [or lightening] products have independently decided to further assure proper use of these products.

These guidelines represent a combination of labeling language proposed by the Food and Drug Administration and new language defined independently by the industry members of the NDMA Hydroquinone Task Group. The result is a comprehensive label that takes into account all aspects of product application and thus helps to ensure safe and effective use of OTC skin discoloration lighteners.

Key aspects of the new guidelines include directions to consumers to:

1. Apply a small amount as a thin layer only to affected areas of dark brownish skin discoloration;

2. Discontinue use after the discoloration is gone;

3. Apply again only if the discoloration reappears;

4. Stop use if any skin irritation becomes severe or any darkening in some users persists;

5. Do not use with other topical products containing resorcinol, phenol, or salicylic acid;

6. Do not apply to inflamed or broken skin;

7. Test overnight on a small section of their skin inside their elbow, if their skin is sensitive.

The use of the word, "discoloration," in the description of these products (e.g., skin discoloration lightener or skin discoloration fade cream) emphasizes that the use of these products is intended only on affected areas of skin discoloration. References to skin tone, even color, or moisturizing must be in the context of limited areas of over pigmentation.

Under this voluntary guideline, manufacturers and distributors would also comply with other general labeling provisions developed under the OTC Review as well as pertinent Voluntary Codes and Guidelines of the Nonprescription Drug Manufacturers Association.

Appended to this guideline are the following:

A. Sample Label "A" of the Voluntary Guideline: Combination Products Containing 2% Hydroquinone and a Sunscreen

B. Sample Label "B" of the Voluntary Guideline: Single Ingredient Products Containing 2% Hydroquinone

These sample labels are intended as examples only. Format and content changes that may be permitted under the regulations pertaining to the marketing of OTC products under the OTC Review will apply for participants in this voluntary industry program.

Nonprescription Drug Manufacturers Association

Hydroquinone Task Group

Sample Label "A": 2% Hydroquinone Plus a Sunscreen

FRONT PANEL

See New Label

Skin Discoloration Fade Cream
TRADE NAME

Net Content With Sunscreen

BACK PANEL

Indications. For the gradual fading of discolorations in the skin such as freckles, age and liver spots or pigment in the skin that may occur as a result of pregnancy or from the use of oral contraceptives. Contains a sunscreen to help prevent darkening from reoccurring.

Directions. Adults: Apply a small amount as a thin layer only to affected areas of dark brownish skin discolorations. Apply twice daily, or use as directed by a doctor. Do not apply to inflamed or broken skin. After discoloration is gone, discontinue use. Apply again only if discoloration reappears. The fading action of this product may not be noticeable when used on very dark skin. If your skin is sensitive, test overnight on a small section of your skin inside your elbow. Children under 12 years of age: Do not use unless directed by a doctor.

Sun exposure should be limited by using a sunscreen agent, a sun blocking agent, or protective clothing to cover lightened skin after treatment is completed in order to prevent darkening from reoccurring.

Warnings. Avoid contact with eyes. Some users of this product may experience a mild skin irritation or temporary darkening. If skin irritation becomes severe or darkening persists, stop use and consult a physician. If no improvement is seen after 3 months, discontinue use. Do not use on children under 12 years of age unless directed by a doctor. This product is not for use in the prevention of sunburn.

Drug Interaction. Do not use this product in combination with externally applied products containing resorcinol, phenol, or salicylic acid, unless directed by a doctor.

Active Ingredient. 2% Hydroquinone and Sunscreen Active

Inactive Ingredients. Listed.

KEEP OUT OF REACH OF CHILDREN

Man./Dist. Name/Address Lot no.

Nonprescription Drug Manufacturers Association

Hydroquinone Task Group

Sample Label "B"
Single Ingredient Product Containing 2% Hydroquinone

FRONT PANEL

See New Label

Skin Discoloration Fade Cream
TRADE NAME

Net Content

BACK PANEL

Indications. For the gradual fading of discolorations in the skin such as freckles, age and liver spots or pigment in the skin that may occur as a result of pregnancy or from the use of oral contraceptives.

Directions. Adults: Apply a small amount as a thin layer only to affected areas of dark brownish skin discolorations. Apply twice daily, or use as directed by a doctor. Do not apply to inflamed or broken skin. After discoloration is gone, discontinue use. Apply again only if discoloration reappears. The fading action of this product may not be noticeable when used on very dark skin. If your skin is sensitive, test overnight on a small section of your skin inside your elbow. Children under 12 years of age: Do not use unless directed by a doctor.

Sun exposure should be limited by using a sunscreen agent, a sun blocking agent, or protective clothing to cover treated skin when using and after using this product in order to prevent darkening from reoccurring.

Warnings. Avoid contact with eyes. Some users of this product may experience a mild skin irritation or temporary darkening. If skin irritation becomes severe or darkening persists, stop use and consult a physician. If no improvement is seen after 3 months, discontinue use. Do not use on children under 12 years of age unless directed by a doctor.

Drug Interaction. Do not use this product in combination with externally applied products containing resorcinol, phenol, or salicylic acid, unless directed by a doctor.

Active Ingredient. 2% Hydroquinone

Inactive Ingredients. Listed.

KEEP OUT OF REACH OF CHILDREN

Man./Dist. Name/Address Lot no.

APPENDIX B

Survey Questionnaire

Physician Survey on Ochronosis

As part of an ongoing review, pharmaceutical manufacturers, in cooperation with the American Academy of Dermatology, are asking AAD members to answer a series of brief questions on their medical experience with ochronosis. This questionnaire contains 7 questions and should take less than 5 minutes to complete.

This questionnaire asks for no patient identifiers, and your name will not be used in the compilation and presentation of the final survey results.

An AAD Committee has reviewed this questionnaire and urges AAD members to provide the requested information.

INSTRUCTIONS

1. Read the introductory paragraphs entitled "Definition of Terms."
2. Complete the survey questions.
3. Mail the completed form in the enclosed self-addressed envelope.

Definition of Terms

Exogenous ochronosis is a deep, bluish or slate gray discoloration of the skin, usually the face, due to exposure to exogenous chemicals. In the early stages, the skin texture is coarsened but in later stages, black, caviar-like papules and pits may be seen within the hyperpigmented areas. Differential diagnosis includes post-inflammatory hyperpigmentation, argyria, hemochromatosis, Addison's disease, porphyria, pellagra, and endogenous ochronosis. A definitive diagnosis can be made by the microscopic demonstration of yellow-brown (ochronotic) deposits within the dermis.

Endogenous ochronosis, on the other hand, is a metabolic disorder unrelated to chemical exposure. It is a systemic, autosomal recessive disorder due to the absence of the enzyme homogentisic acid oxidase. Homogentisic acid accumulates and may polymerize in connective tissue, resulting in bluish-gray discolorations found in the conjunctiva, cornea, eyelids, sclera and pinnae; in areas rich in sweat glands; and in areas where cartilage or tendons have a thin covering of skin, including ears, nasal tip and hands.

Survey questions appear on reverse side of this page

S-1603

PLEASE READ INSTRUCTIONS ON REVERSE SIDE BEFORE RESPONDING

1. In what type of practice do you participate?

(114) 1☐ Solo 2☐ Group 3☐ University based referral 4☐ Other_____
(please specify) 115

2. The approximate number of patients seen in your practice per year is:

_____# of patients per year
116–9

3. The total number of patients in your practice is: _____ total # of patients
20–3

4. For how many years has your practice been in existence? _____# years
24,5

5. How would you describe the demographics of your practice of dermatology?

_____% White _____% Black _____% Hispanic _____% Asian
26–8 29–31 32–4 35–7

6. How many cases of ochronosis have you diagnosed in your practice of dermatology?

EXOGENOUS ochronosis _____ cases
38–40

ENDOGENOUS ochronosis _____ cases → Continue with Q.7
41–3

44 ☐ I have diagnosed no cases to date of ochronosis → Go to Q.8

7. Of the cases of EXOGENOUS ochronosis,

a. What were the approximate dates (specify year) of these cases?

_____
45,6 47,8 49,50 51,2 53,4

b. How many of your cases were confirmed by biopsy? _____# of cases
55–7

c. Were you the only attending physician? 1☐ Yes 2☐ No (158)

d. Are medical records available for these cases? 1☐ Yes 2☐ No (159)

e. Did you review medical records in providing answers to this survey? 1☐ Yes 2☐ No (160)

f. What was (were) believed to be the causative agent(s) for your cases of exogenous ochronosis?

_____ _____

_____ _____
61 62 63 164

8. ***Thank you for completing the questionnaire. Please send the completed questionnaire in the enclosed self-addressed envelope.***

_____
Name/Address *Date*

APPENDIX C

Appendix C Tables:

APPENDIX C

Table C-1: Number of Years in Practice: Percentage of Physicians Who Have and Have Not Treated Exogenous Ochronosis

Number of Years	Total Physicians %	MDs Who Have Tx Cases %	MDs Who Have Not Tx Cases %
1-5	26	25	26
6-10	18	22	17
11-15	17	18	17
16-20	15	12	15
21-25	9	7	10
26-30	7	7	7
31-45	5	3	5
≥ 46	1	1	1
No Answer	2	5	2
	100	100	100
Median Number	12	11	12

APPENDIX C

Table C-2: Number of Years in Practice: Percentage of Physicians Who Have Reportedly Diagnosed/Treated One or More, Two or More Five or More Cases of Exogenous Ochronosis

	MDs Who Reportedly Diagnosed/Treated:		
Number of Years:	≥1 Cases %	≥2 Cases %	≥5 Cases %
1-5	25	20	11
6-10	22	25	32
11-15	18	18	14
16-20	12	10	11
21-25	7	9	11
26-30	7	6	7
31-45	3	5	11
≥ 46	1	2	-
No Answer	5	6	4
	100	100	100
Median Number	12	11	12

APPENDIX C

Table C-3: Type of Practice: Percentage of Physicians Who Have Reportedly Diagnosed/Treated One or More, Two of More, Five or More Cases of Exogenous Ochronosis

	MDs Who Reportedly Diagnosed/Treated:		
Practice:	Cases %	≥1 Cases %	≥2≥5 Cases %
Solo	45	44	61
Group	31	34	14
University-based Referral	20	19	25
Other	4	3	-
	100	100	100
Base (Total MD)	(222)	(104)	(28)

APPENDIX C

Table C-4: Number of Patients Seen Per Year: Percentage of Physicians Who Have or Have Not Treated Cases of Exogenous Ochronosis

Number of Patients	Total Physicians %	MDs Who Have Tx Cases %	MDs Who Have Not Tx Cases %
< 1,000	3	3	3
1,000-1,999	5	6	5
2,000-2.999	7	7	7
3,000-3,999	7	9	7
4,000-4,999	9	11	8
5,000-5,999	15	11	16
6,000-6,999	12	11	12
7,000-7,999	10	7	11
8,000-8,999	6	7	6
9,000-9,999	3	2	3
10,000-14,999	10	11	11
15,000-19,999	2	2	1
≥ 20,000	3	4	3
No Answer	8	9	7
	100	100	100
Median Number	6,000	5,000	6,000
Base (Total MDs)	(2,108)	(222)	(1,886)

APPENDIX C

Table C-5: Total Number of Patients in Practice: Percentage of Physicians Who Have and Have Not Treated Cases of Exogenous Ochronosis

Number of Patients	Total Physicians %	MDs Who Have Tx Cases %	MDs Who Have Not Tx Cases %
< 1,000	2	2	2
1,000-4,999	10	12	10
5,000-9.999	10	8	11
10,000-14,999	9	7	9
15,000-19,999	6	4	6
20,000-29,999	9	12	9
30,000-49,999	8	8	7
≥ 50,000	6	7	6
No Answer	40	40	40
	100	100	100
Median Number	13,000	15,000	13,000
Base (Total MDs)	(2,108)	(222)	(1,886)